A General Model for the Transmembrane Proteins of HIV and Other Retroviruses

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ABSTRACT

A hypothetical model of the transmembrane (TM) protein of human immunodeficiency virus (HIV) is proposed that is derived from the known structure of the influenza TM protein HA_2. This model is consistent with computer algorithms of predicted protein structure and with known properties of TM proteins determined by sequence homology, site-directed mutations, peptide analogs, immunochemistry, or other biologic means. It is applicable to a wide variety of retroviral TM proteins differing widely in overall molecular weight.

INTRODUCTION

THE RETROVIRUSES COMPRISE a diverse family of viruses, each with a narrow host range but causing a variety of infections. Comparison of the structural and functional similarities among members of this virus family continues to provide insights into a number of biologic, immunologic, and pathogenic mechanisms. Many retrovirus genomes have been sequenced in their entirety, inviting comparisons of homologous genes and proteins. Most of these studies have concentrated on highly conserved regions, with the generation of phylogenetic trees.[1]

Among the retrovirus gene products, the envelope protein is the most diverse in size and sequence. Although the *env* gene product is in all cases synthesized as a precursor that is subsequently cleaved into a surface attachment subunit (SU) and a membrane-anchoring TM subunit, there is otherwise little conservation between even closely related branches of the virus family.[1–3] Limited comparison of functional regions has been attempted using computer-based methods, such as hydropathy plots, sequence homology, and algorithms for predicting protein structure.

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Beginning with the premise that functionally homologous viral proteins have a generally common structure, we have decided to initially step back from computer models and begin by searching for certain benchmark features that may bring order to this protein diversity. We have chosen the TM protein since it is the more conserved of the two subunits in the heterodimer.[4] Several features of HIV gp41 have been functionally defined by mutation, studies with peptide analogs, and, in the case of the fusion peptide, by sequence homology with another virus family.[5-9] With such structural and functional benchmarks in place, it is possible to design a model for the TM protein consistent with known biologic information, extendable across the whole virus family, and homologous to the known structure of the well-characterized TM protein HA_2 of influenza virus.[10]

METHODS

Sequences and computer analysis

Peptide sequences were obtained either directly from published sequences or from computer translations of DNA sequences available through GENBANK by the IBI Pustell Sequence Analysis program. Single-letter codes are used for amino acids.[5] Cited retrovirus sequences include that for the HXB2-BH10 provirus of HIV-1, equine infectious anemia virus (EIAV), human T cell lymphotrophic virus, type 2 (HTLV-2), visna virus, Mason-Pfizer monkey virus (MPMV), feline leukemia virus (FeLV), mouse mammary tumor virus (MMTV), and Rous sarcoma virus (RSV).[11-18] The peptide sequence for influenza virus is that obtained for the A/H3N2 Australia-Victoria 75 strain.[19]
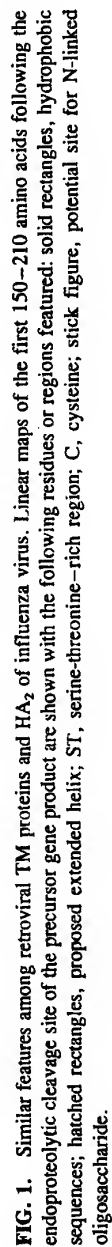
Each TM protein sequence was analyzed by the Hopp-Woods and Kyte-Doolittle algorithms ($n = 6$) for hydropathy, by the Chou-Fasman and Garnier algorithms for protein structure, available through the IBI Pustell or Intelligenetics PC Gene suite of programs, and by the Parker et al. and Margolit programs for prediction of T and B cell reactive sequences.[20-26] Structural features are compatible with computer-generated potentials for β sheet (P_b), α helix (P_a), extended chain (P_e), coil (P_c); and reverse turns (P_t), which were critically evaluated and generally followed when the probability for a given structure significantly exceeded others. Minor variations among different retroviruses and computer algorithms were readily reconciled and adaptable to a consensus structure for the virus family without substantive conflict with the predicted structure. However, keeping in mind the limits of such algorithms to predict actual structure, we have biased the model whenever the algorithm may only slightly favor one alternative structure, based on known biologic information, the overall characteristics of the influenza model, or other biochemical considerations.

RESULTS

Common structural features among retrovirus TM proteins

Examination of the sequence of the TM proteins from all the major phylogenetic branches of the retrovirus family reveals that the amino-terminal 200 amino acids have a number of conserved structural characteristics, as illustrated for eight representative viruses in Figure 1. After cleavage from the precursor envelope gene product at a RXK/RR site, each has an extended hydrophobic region at or near the amino terminus, from 13 to 24 amino acids in length.[27] In HIV this region is the fusion peptide, confirmed by either mutation or peptide analogs that inhibit HIV-induced fusion.[5,8] This region is usually closely followed by a stretch of 8–17 amino acids enriched in S and T, which in HIV has been implicated as critical for the noncovalent binding of gp41 to the SU protein gp120.[5] This in turn is followed by a region with propensity for an extended α helix, according to the Chou-Fasman algorithms. The next readily identifiable region is marked by two or three vicinal cysteines beginning at position 81–90. In the oncoviruses this region is highly conserved and immunosuppressive, and in the lentiviruses HIV and EIAV this peptide comprises the principal epitope recognized by antibody to the transmembrane protein.[6,7,15,28,29] This region we therefore term the immunodominant region. This is followed by a conserved glycosylation site. Finally, a second hydrophobic sequence, beginning at position 122–152 and extending 19–27 amino acids, has been identified as the probable membrane-spanning region and anchors both the SU and TM proteins of the

FIG. 1. Similar features among retroviral TM proteins and HA$_2$ of influenza virus. Linear maps of the first 150–210 amino acids following the endoproteolytic cleavage site of the precursor gene product are shown with the following residues or regions featured: solid rectangles, hydrophobic sequences; hatched rectangles, proposed extended helix; ST, serine–threonine–rich region; C, cysteine; stick figure, potential site for N-linked oligosaccharide.

heterodimer to the viral envelope.[30] Beyond this region retroviruses are widely disparate, accounting for the large differences in molecular weights of the TM proteins, with from 20 to 226 additional amino acids beyond this hydrophobic segment.

Parallel structures in retrovirus and influenza virus TM proteins

The HA_2 glycoprotein of influenza virus shares a number of these properties, some of which have been reported previously.[31] It begins, after cleavage at an REKR site, with a hydrophobic amino terminus that has been identified as its fusion peptide.[32] The next peptide region has been identified as important in the interaction of HA_2 with its attachment protein HA_1.[33] HA_2 contains a region with vicinal cysteines immediately followed by a potential glycosylation site. The preceding sequence has been determined to be highly fibrous, with an extended α helix some 54 amino acids long. Finally, through its membrane-spanning region it anchors both itself and HA_1, its partner polypeptide of the heterodimer, to the viral envelope. In view of these overall similarities, we thought it reasonable to construct a model of the retroviral TM protein using the known structure of influenza HA_2 as a scaffold.

Structural model of the TM protein of HIV

Such a model, with each amino acid identified, is projected for HIV-1 gp41 in Figure 2. Overall, the TM protein is projected to be a fibrous structure with a significant degree of sidedness, all the immunodominant and glycosylation regions being located at the apex and left side of the protein. Several specific features emerge upon examination of this model. The laterally extended amino terminus bears the fusion peptide, including the hydrophobic core LFLGFL, with potential as a membrane insertional hairpin similar to the hydrophobic core of signal sequences.[34,35] This is followed by an internally looping structure rich in S and T (5 of 11) and interactive with gp120 and an ascending extended helix of 38 amino acids.[5] The apex is comprised of the vicinal cysteines and the immunodominant region of the protein and is succeeded by an extended glycosylated region, with localized propensity for α helix and a bend rich in S and T (4 of 7) also interactive with gp120.[5-7,29] Next is an extraordinarily highly charged region (12 of 13 are E, K, Q, or N), which probably forms an α helix stabilized by multiple "ion pairs."[36] Finally, the highly hydrophobic membrane-spanning region is depicted as an α helix with a sharp turn just after emerging from the lipid bilayer.

Certain features emerge naturally from the computer analyses. At the apex of the polypeptide, a strong turn is indicated just where appropriate to allow internal disulfide bond formation between the vicinal cysteines. All glycosylation sites are at predicted turns or extended chains. Other features are proposed in light of the precedent of the influenza virus structure or existing biologic information. The fusion peptide by computer analyses alone has been predicted to span the membrane.[37] It is shown here to be external to the lipid bilayer, where it may freely interact with its presumed cellular target, consistent with recent findings indicating that this hydrophobic sequence lacks a stop transfer signal.[38] The accessibility of the amino-terminal hydrophobic peptide is also supported by the observation that 75% of horses infected with another lentivirus, EIAV, produce antibodies reactive with the corresponding region of EIAV gp45.[29] It is shown as a loosely coiled structure, similar to the known fusion peptide structure of influenza HA_2.[10] Computer models indicate a β structure for this region in most retroviruses, consistent with Chou-Fasman algorithms of such a strongly hydrophobic segment, but no strong turns are predicted that would produce a tight hairpin structure. The immunodominant region is so designated because of preponderant immunochemical evidence, even though computer analyses project other regions (such as the highly charged segment) as principal B or T cell epitopes.[6,7,28,29]

Fibrous amphipathic core of retrovirus TM proteins

A central structure of the model is the extended α helix proposed just before the immunodominant region of the molecule. Helical net analysis of this region, shown in Figure 3, indicates that it has a propensity to
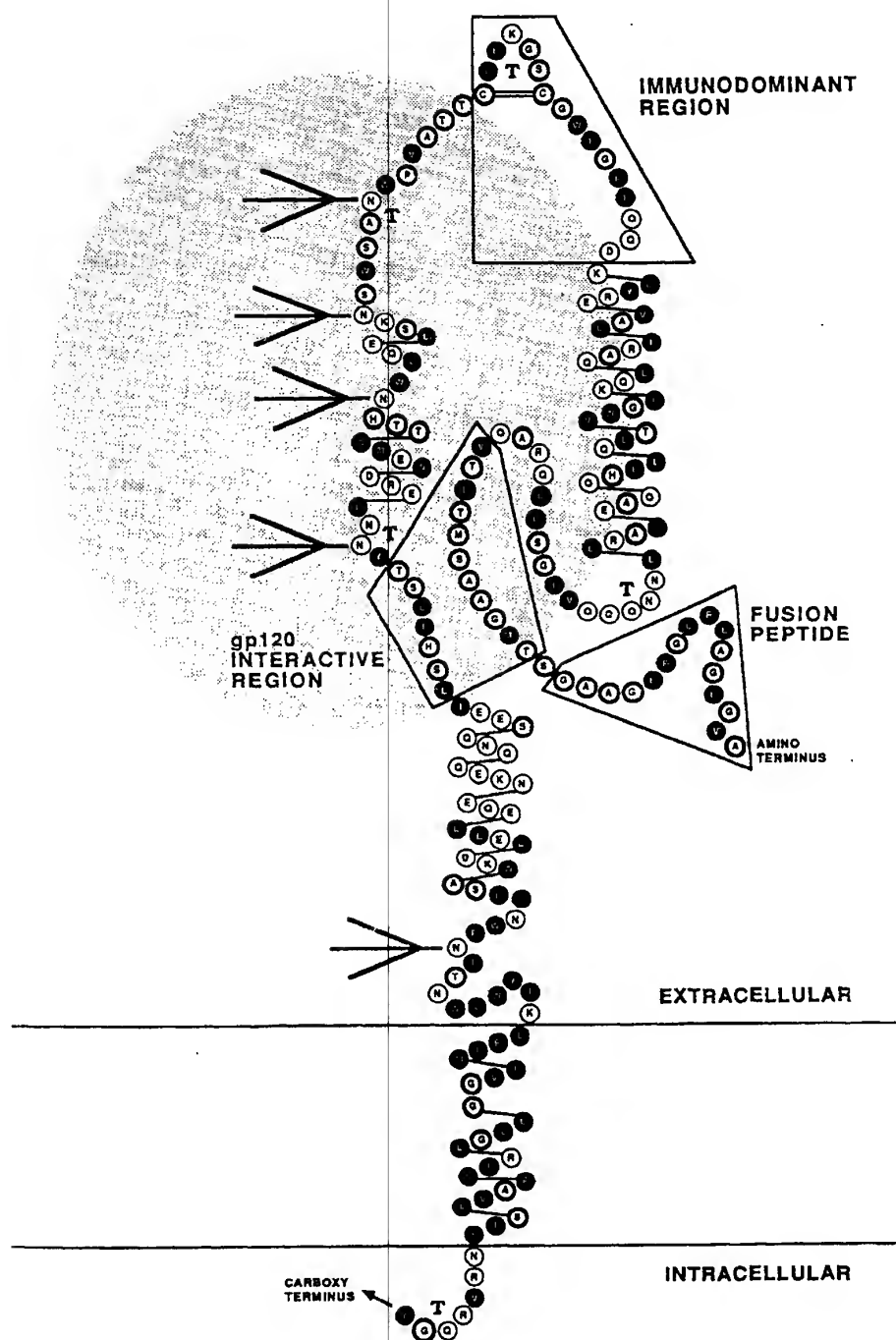
FIG. 2. Model of gp41 (TM) protein of HIV-1. A linear sequence of gp41 is shown in a planar projection of the proposed structure derived from computer modeling and based on the influenza HA₂ scaffold. α Helices are depicted as modified helical nets alternating three and four amino acids per turn connected by single lines. Hydrophobic amino acids are indicated as solid circles, charged amino acids as open circles, and neutral amino acids as partly filled circles. Nonhelical regions are shown as loosely coiled extended chains; strong turns are indicated by T; the proposed intramolecular disulfide bond by a double line; potential glycosylation sites by stick figures.
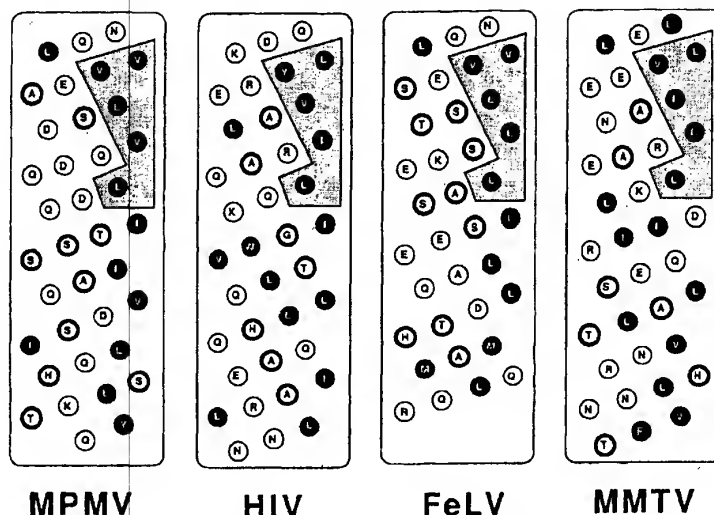
FIG. 3. Helical net analysis of retroviral TM protein segments. Similar regions of the TM proteins of MPMV (Q427–N464), HIV-1 (N553–Q590), FeLV (R469–N503), and MMTV (T490–L527) are shown as helical net projections, with a constant hydrophobic environment highlighted.[39]

be amphipathic, with a hydrophobic moment over 11 helical turns of 0.35. This propensity is even more strongly indicated in other retroviruses and is common to the entire virus family. Indeed, over 25 residues and eight helical turns in FeLV, all 10 of the hydrophobic amino acids lie at 0–160° on a helical wheel, but seven of the eight charged residues lie at 180–300°. A specific conserved feature in oncoviruses of groups B, C, and D, as well as lentiviruses, is the hydrophobic environment highlighted in Figure 3, which is maintained despite a great degree of sequence diversity among these viruses.

Model of conserved structures among retrovirus TM proteins

The general features of the model are equally valid for other retroviruses, with minor variations to adapt the structure to a wide variety of disparate sequences. Shown in Table 1 are the potentials from Chou-Fasman secondary structure predictions for the proposed conserved structural features among these TM proteins. The data are consistent with the proposed consensus structure and comparable to the potentials for influenza HA_2, in which the extramembranal structures have been established by crystallography. For the extended helical segment, P_a exceeds P_b except in one instance. Although some α and β potentials appear quite similar, when other factors are considered the propensity for α helix is significantly increased. The Chou-Fasman prediction method does not take into account the periodic occurrence of hydrophobic residues characteristic of amphipathic helices but scores all hydrophobic residues as strong β formers. Since peptide segments within the extended helix have a significant amphipathic score of 20–40 and given that this score is a measure of the amphipathic helical character of the segment, this supports proposal of helical nature for this region. Even though there are short segments with β potential, the likelihood of continuing helix formation following nucleation is high, and the probability of the helix abruptly halting in the absence of a helix breaker tetramer is very low.

Also shown in Table 1 are the potentials for the proposed conserved turns. For the turn immediately preceding the extended helix, P_t varies from 0.990 to 1.325; values above 1.000 are frequently considered predictive of β turns. In addition, the turn potentials of the conserved turn within one to four amino acids of the vicinal cysteines are listed, with P_t values of 1.050–1.298. The potentials of the proposed conserved

TABLE 1. COMPUTER-GENERATED CHOU-FASMAN POTENTIALS FOR CONSERVED HELIX AND TURNS IN TM PROTEINS

Virus	Turn preceding helix			Extended helix			Vicinal cys, no.	Posthelix turn			Turn inside membrane		
	No. aa	aa	Pt	No. aa	Pa	Pb	aa	No. aa	aa	Pt	No. aa	aa	Pt
HIV-1	39–42	QQNN	1.270	43–80	1.162	1.146	87, 83	87–90	CSGK	1.298	197–200	RQGY	1.158
EIAV	46–49	NSTL	1.135	50–84	1.139	1.046	91, 99	100–104	HTGH	1.105	193–196	TSSP	1.203
Visna	28–31	QQSY	1.133	32–86	1.155	1.061	90, 96	87–90	DCWH	1.050	202–205	QAYK	0.948
HTLV-2	30–33	SSKS	1.325	34–65	1.095	1.091	81, 88	76–79	EQGG	1.210	158–161	LPQR	0.870
MPMV	18–21	STGT	1.153	32–65	1.066	1.077	81, 88	76–79	EQGG	1.210	154–157	NKLM	1.138
FeLV	24–27	GTGT	1.260	28–66	1.161	0.965	86, 93	81–84	QEGG	1.210	172–175	DRIS	0.995
MMTV	40–43	HRNV	0.990	44–82	1.156	0.999	86, 94	89–92	NRDF	1.190	200–203	VQSD	1.090
RSV	17–20	GPTA	1.175	21–65	1.091	1.034	90, 97	95–98	GMCC	1.135	172–175	VSSS	1.198
FLU-HA₂	70–73	FSEV	0.935	76–130	1.117	0.953	136, 142	133–136	GNGC	1.468	212–215	QRGN	1.262

turn immediately inside the lipid bilayer vary most widely, with values of 0.870–1.203, but several exceed 1.10, including strong turn propensities for HIV, as depicted in Figure 2, and for EIAV.

Schematic projections are shown for several representative retroviruses in comparison with HA₂ of influenza virus in Figure 4. In a much smaller TM protein, such as gp15 of HTLV-2 or of MPMV, both the ascending helix and the descending coil are truncated relative to HIV, but the overall structural features are consistent with the model. In other viruses the ascending helix may be broken into multiple helical segments. The most variable region is the segment "descending" from the immunodominant apex to the site of membrane insertion. The number of glycosylation sites, position and length of helix, and the number or position of turns all vary significantly. The principal constants of the model throughout the virus family are
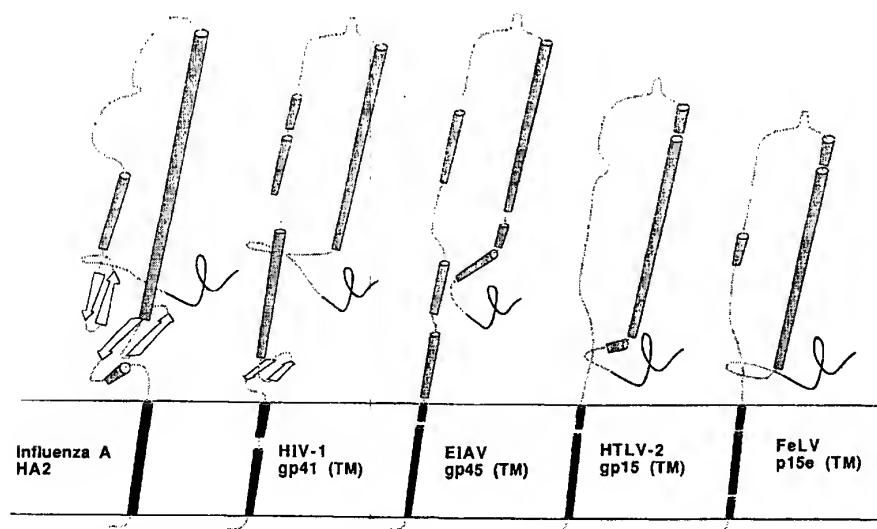

FIG. 4. Schematic predicted structures of TM proteins of retroviruses and influenza virus. Solid cylinder, membrane-spanning helix; cross-hatched cylinder, extramembranous α helix; directional arrows, β sheet; solid line, fusion peptide; broken line, extended chain or random coil. Influenza HA₂ structure is modified from that previously published.[10]

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the fusion peptide, the proposed amphipathic ascending helix, the immunodominant region, the strong turn just interior to the lipid bilayer, and the extramembranal mass of the protein before the membrane-spanning region.

DISCUSSION

Although any model proposed in the absence of x-ray crystallographic data is of its very nature speculative, it is useful in exploring the potential similarity of these viruses to other families of enveloped viruses and in delineating regions that may serve common functions across the retrovirus family. A prime example is the region we propose as the extended, amphipathic, α helical fiber. Its potential importance is underscored by an HIV mutant (A 582 to T) that abrogates antibody neutralization of HIV at distant epitopes, presumably by conformational changes in the heterodimer, even as it decreases the helical potential of this region.[39] Such helical fibers have been identified as the structural backbone in HA_2 of influenza virus, the peplomeric protein of coronaviruses, and the hemagglutinin of reovirus.[10,40,41] The glycoprotein heterodimers of retroviruses form multimers, possibly by hydrophobic bonding along such fibers to form coiled coil structures.[42,43] Mutation in this structure may disrupt the organization of the virion and its antigenic properties. Amphipathic helices are also recognized as key structural features for antigen interaction with T cells, particularly when in close proximity to epitopes recognized by B cells. Thus, the model predicts this region to be important in T cell recognition of HIV and other retroviruses, although other helical segments are predicted to have such potential and may also play a role. Such possibilities are strengthened by the finding that in the oncoviruses the peptide region just downstream from the proposed helical region also has potential for interaction with T cells, bearing similarity to interleukin-2 and being immunosuppresive.[15,28]

The model thus provides a structural context in which unique regions of the TM protein can be identified and directly compared across the entire virus family, predictions made concerning function, and these predictions tested by site-directed mutations.

ACKNOWLEDGMENTS

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